COVER SHEET

NMR study of the association of propofol with nonionic surfactants

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17th December 2002

Running title: Propofol and Nonionic Surfactants

Keywords: nonionic surfactants, pulsed field-gradient spin-echo (PFG SE) NMR spectroscopy, diffusion, ^{1}H NMR longitudinal relaxation, molecular association, micellization, solubilization, microemulsions, drug delivery, Solutol HS15, Poloxamer 407, Poloxamer 188, Polysorbate 80, Cremophor EL, Diprivan®, propofol, 2,6-diisopropylphenol

Abbreviations: EO, ethylene oxide; HS, 12-hydroxystearate; NOE, Nuclear Overhauser effect; NOESY, Nuclear Overhauser effect spectroscopy; PEO, poly(ethylene oxide); PFG, pulsed field gradient; PPO, poly(propylene oxide); SE, spin echo; T_1, longitudinal relaxation time.

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Abstract

The general anesthetic 2,6-diisopropylphenol (propofol) is very poorly soluble in water and is normally administered in the form of an emulsion. We demonstrated that several commercially available nonionic surfactants (Tween 80, Cremophor EL, Poloxamer 188, Poloxamer 407, Solutol HS15, and Vitamin E TPGS) render propofol soluble with a specific solubilization capacity of at least 0.1 g/g. The room-temperature stability of the solutions appeared to be limited only by the chemical stability of the compounds involved. The association between propofol and the surfactants was investigated by various NMR approaches, including measurements of diffusion coefficients, ^{1}H longitudinal relaxation times, and the magnitude of intermolecular nuclear Overhauser effects. The results were consistent with the micellar solubilization mechanism of propofol by the surfactants (unimer solubilization in the case of Poloxamer 188). ^{1}H longitudinal relaxation and diffusion behavior of propofol were monoexponential in each case. Solubilization caused a considerable shortening of propofol's proton T_1's. The values of the diffusion coefficient of propofol were several percent higher than those of surfactants. This was explained by the partitioning of propofol between swollen micelles and the aqueous solution. Diffusion measurements also revealed the presence of a rapidly-diffusing ethylene oxide population in surfactant solutions, which is consistent with free poly(ethylene oxide) (PEO) known to be present in commercially produced surfactants. The free PEO blocks exhibited molecular association with the extramicellar propofol.

1 Introduction

Propofol (2,6-diisopropylphenol) is a commonly used general anesthetic. In clinical practice it is administered intravenously. It is dispensed as an isotonic oil-in-water emulsion at a concentration of 1% (w/v) that is formulated with glycerol, soya oil, sodium hydroxide, egg lecithin, and disodium EDTA and has a pH of 6 to 8.5.[1,2]

The goal of this work was to investigate the association between propofol and six nonionic polymeric surfactants: Poloxamer 407 (F127); Poloxamer 188 (F68); Tween 80; Solutol HS15; Cremophor EL; and Vitamin E TPGS. The principal components of Poloxamers are triblock copolymers of the general form $EO_{n1}PO_mEO_{n2}$, where EO = ethylene oxide and PO = propylene oxide. The average composition {n1, m, n2} is {97, 69, 97} to {100, 65, 100} for F127 and {76, 29, 76} for F68; their average molecular weights are 12600 and 8400, respectively.[3–7] Cremophor EL (average MW$\sim$2500) is polyethoxylated castor oil, a complex mixture of surfactants with the main component being poly(ethylene glycol)(35) glycerol triricinoleate.[8] The principal components of the other surfactants are: Solutol HS15, poly(ethylene glycol)(15) 12-hydroxystearate (MW$\sim$960); Vitamin E TPGS, α-tocopheryl poly(ethylene glycol)(22) succinate (MW$\sim$1500); Tween 80 (Crillet 4 HP, Polysorbate 80), *tris*-poly(ethylene glycol)(20) sorbitan monooleate (MW$\sim$1300).[9,10] The principal criterion for the choice of surfactants for this study was their biocompatibility and pharmacological properties, briefly discussed below in this Section. All of the surfactants contain free poly(ethylene oxide) (PEO) which is often added purposefully to facilitate the industrial handling of the compounds.

Of the above list, Poloxamers are probably the most studied and the best understood,

and have been extensively reviewed in the literature.[6] Poloxamers 407 and 188 are also available under the names Lutrol F127 (Pluronic F127) and Lutrol F68 (Pluronic F68), respectively. Lutrol is the clinical grade of Poloxamers, extensively used in the pharmaceutical industry. The PEO and the PPO blocks are usually thought of as hydrophilic and hydrophobic, respectively.[11] Poloxamers are thus amphiphilic block copolymer surfactants with relatively low polydispersity. Variation of the length of each of the blocks enables the modulation of the copolymer properties (such as micellization) in a wide range of their respective values.

In this work, several NMR techniques were applied to investigate the degree and the nature of association between the studied surfactants and propofol. The principal findings were the following. (1) Each of the six surfactants solubilized propofol to at least 1% (w/v) at the 10% (w/v) surfactant concentration. (2) In surfactant solutions, poly(ethylene oxide) exhibited two diffusion coefficients, "fast" (free PEO blocks) and "slow" (micellar PEO blocks bound to the hydrophobic tails). (3) Propofol exhibited a single diffusion coefficient in all cases; its value was consistent with propofol largely being associated with the surfactant molecules or micelles and partly residing in the extramicellar solution. (4) In each system, the proton relaxation times of the solubilized propofol were considerably shorter than those in a $CDCl_3$ solution or in bulk propofol. (5) Although diffusion coefficient measurements are required to fully understand the molecular association in the studied systems, T_1 measurements were used to provide "quick evidence" of molecular association between propofol and the surfactants.

The motivation for this work was, in part, the investigation of alternative delivery vehicles for the intravenous administration of propofol. While the commercially available

emulsion (Diprivan®) provides for an efficient delivery of propofol, it also has disadvantages. Two of these are the presence of residual free propofol in the "water" phase which is believed to lead to pain on intravenous injection,[12] and the propensity of the emulsion to support bacterial growth.[13] In recent years extensive research has been undertaken to develop novel and robust drug delivery vehicles providing for fewer clinical side effects.[14–18] A number of nonionic surfactants appear promising in this regard.[19–21] Although problems with clinical applications of some surfactants (most notably with Cremophor) have been pointed out,[22–24] many are widely used in drug formulations. They are generally acknowledged to have low toxicity and are well tolerated clinically.[25,26] Several compounds containing poly(ethylene oxide) (PEO) moieties have been shown to modulate or reverse multidrug resistance in animal and human cancer cells, with Solutol HS15 and Tween 80 being among the least toxic.[27–29] Solutol HS15 has been shown to interact with plasma lipoproteins,[30] and Poloxamers with brain microvessel endothelial cells.[31] Poloxamers have been shown to enhance the delivery of drugs and ATP to cells[31,32] as well as to affect the distribution of the delivered drug inside the target cell.[33] Targeted drug delivery mediated by Poloxamers conjugated with an antibody has been attempted.[32] Poly(ethylene glycol) coating has been found to increase the bloodstream circulation lifetime of liposomes.[34] All of these features make PEO-containing polymer surfactants particularly interesting as potential components of intravenous drug delivery vehicles.

The range of surfactants studied in this work was not meant to be comprehensive, with Triton and Brij series being two of the notable omissions. However, the methodology presented here is independent of the specific surfactant. The development of a detailed practical example of the application of NMR to a pharmacologically relevant micellar system formed the second part of our motivation. The NMR results described here

are relatively easy to interpret, and the experiments used could provide a basis for a methodology used for the in vitro evaluation of novel drug delivery systems.

2 Experimental

Materials: Surfactants were obtained from the following sources: Tween 80 (Crillet 4 HP, CAS 9005-65-6), from Croda Chemicals (Australia); Cremophor EL (61791-12-6), Poloxamer 188 (106392-12-5), Poloxamer 407 (106392-12-5), Solutol HS15 (61909-81-7), from BASF (Ludwigshafen, Germany); Vitamin E TPGS (9002-96-4), from Eastman Chemicals (Kingsport, TN). The certificates of analysis of the batches used showed that they typically consist of approximately equal amounts of the principal amphiphilic compound and free poly(ethylene glycol), with small ($\sim$5%) quantities of impurities. Propofol (CAS 2078-54-8) was obtained from Archimica SpA (Varese, Italy). $CDCl_3$ was purchased from Aldrich (Milwaukee, WI); CCl_4 (used for magnetic susceptibility matching, spectroscopic grade), from AJAX Chemicals (Auburn, NSW, Australia); D_2O, from ANSTO (Lucas Heights, NSW, Australia). All chemicals were used as received. Water was obtained from a Milli-Q reverse-osmosis apparatus (Millipore, Bedford, MA).

Surfactant solutions: Typical surfactant concentration in the studied systems was 10% (w/v). The solutions were prepared by repeated vortexing and incubation at 35 °C to 40 °C over at least 24 h. Propofol was loaded into the D_2O/surfactant systems using the same cycle. For the solutions of Poloxamers, the preparation procedure included centrifugation at 380$\times$g to facilitate the dissolution of the surfactant. Cloud point and gelation temperatures were estimated visually following the equilibration of samples in a water bath.

NMR spectrometer: A Bruker (Karlsruhe, Germany) DRX-400 spectrometer with an Oxford Instruments (Oxford, UK) 9.4 T wide-bore magnet equipped with a 1000

G cm^{-1} z-only actively shielded diffusion gradient probe was used in the experiments. The general setup of the spectrometer has been described elsewhere.[35–39] The length of the linear-gradient region was 1 cm in the z direction. The probe was equipped with a number of inserts, of which the 10-mm ^{1}H-only and the 5-mm inner-^{31}P, outer-^{1}H inserts were used for the ^{1}H diffusion measurements. ^{1}H 90°-pulse durations were $\sim$20 μs and 40 μs, respectively. NOESY, most of the inversion recovery measurements, and reference 1D measurements were performed using a 5-mm Bruker TXI probe (typical ^{1}H 90°-pulse length, 8 μs). Sample temperature was controlled, where applicable, by air flow at 400 L h^{-1}. Temperature was calibrated separately for each probe using a capillary containing methanol (low-T) or ethylene glycol (high-T).[40,41]

NMR samples: To ensure that the sample in diffusion measurements was completely contained within the probe's constant-gradient region, it was constrained to the length of 8–9 mm. One of the following three setups was used when measuring the diffusion coefficients: (1) 10-mm ^{1}H-only insert, the sample ($\sim$ 0.7 mL) was placed into a cylindrical Wilmad microcell, bubbles were removed by light tapping, and the microcell was placed inside a 10-mm o.d. NMR tube containing 2.5 mL of CCl_4 for magnetic susceptibility matching;[37,39] (2) 10-mm ^{1}H-only insert, the sample (0.7 mL) was placed into a 9-mm o.d. flat-bottom NMR tube, a 13-mm long Teflon susceptibility plug was placed above the sample, and the tube was inserted into a 10-mm o.d. NMR tube containing 1.5 mL of CCl_4 for magnetic susceptibility matching; (3) 5-mm inner-^{31}P, outer-^{1}H insert, the sample was placed into a 5-mm o.d. Shigemi tube (BMS-005B, susceptibility-matched for D_2O), the sample's length was restricted by the susceptibility-matching rod. The typical shimming linewidth was 8–10 Hz in setups (1) and (2) and 3–5 Hz in (3). When the TXI probe was used, either the standard Wilmad 528-PP NMR tubes or the susceptibility-matched Shigemi tubes were used;

the residual linewidth was ∼3 Hz in both cases. NMR spectra, diffusion coefficients, and longitudinal relaxation times were measured at 23 °C. No chemical shift standard was added, to obviate the possibility of it interacting with the micelles. Chemical shift referencing was done on the HDO peak (set to 4.8 ppm). A small amount of $CDCl_3$ (∼15% v/v) was added to bulk propofol samples for the lock signal.

NMR Measurements: A convection-compensating PGSE pulse sequence[42] was used for most diffusion measurements. Some of the room-temperature measurements were carried out using the non-compensated PGSE sequence. Typically, 32 linearly incremented values of g were used in a diffusion measurement. Trapezoidal gradient pulses were used (ramped in 10 steps, ramp duration 0.1 or 0.5 ms; the exact value had no identifieable effect on the quality of the measured data). The absence of convection effects was established by comparing the results of measurements carried out with different values of the diffusion time (e.g. 8 ms and 20 ms). Longitudinal relaxation times, T_1, were measured using a standard inversion recovery pulse sequence. NOESY spectra were acquired using either the standard[43] or gradient-selected[44] phase-sensitive pulse sequence. Data processing is described in detail elsewhere.[35,45] The spectra of bulk propofol were recorded with an appropriately detuned Bruker TXI probe. The absence of radiation damping effects was checked by using a modified inversion-recovery pulse sequence, $\pi/2 - \tau - \pi/2$. In the determination of relaxation times and diffusion coefficients of micellar propofol, particular attention was paid to baseline correction of the spectra in order to avoid distortions of the measured intensities of the inherently small propofol peaks. In most cases, polynomial baseline correction (0th–2nd order) was sufficient. In some cases, cubic-spline correction was used.

3 Results

Proton NMR spectra of all the surfactant solutions in D_2O were similar in that in each of these the largest peak was that near 3.7 ppm corresponding to the CH_2 groups of poly(ethylene oxide) (PEO) and poly(isopropylene oxide) (PPO), as well as the CH protons of PPO. This peak was inhomogeneously broadened in all samples, and its lineshape depended on the presence of propofol in the system. Other prominent peaks, common to all or several of the compounds, were near 0.9 ppm from CH_3 groups (1.2 ppm for PPO CH_3 groups) and (except for the Poloxamers) near 1.3 ppm from aliphatic CH_2 groups. Representative spectra of three of the surfactants are shown in Figure 1.

Propofol solubilization: initial observations. The structure of propofol and the ^{1}H NMR spectrum of its solution in $CDCl_3$ are shown in Figure 2. T_1 values of its protons in the $CDCl_3$ solution ranged from 1.7 s for the methyl groups to 3.6 s for the aromatic proton in *para*-position to the OH group. T_1's in bulk propofol were approximately half these values.

All of the surfactant solutions solubilized propofol. At room temperature, a 10% (w/v) solution of each surfactant was capable of solubilizing propofol to at least 1% (w/v) concentration, which corresponded to a specific solubilization capacity of 10%. The solutions were clear, had pale to intense yellow color, and showed no opalescence. They did not appear to "age"; all of them were chemically and physically stable for at least 2 months at room temperature and at least 1 year at 4 °C. The F68 solution of propofol formed a dark-yellow precipitate at 4 °C; however, a brief room-temperature vortexing restored the system and its NMR behavior to the original state. The other

solutions remained homogeneous liquids when cooled to 4 °C. We estimated clouding point or gelation temperature of each of the six systems containing 1% (w/w) propofol and 10% (w/w) surfactant in D_2O-saline (P/S/D_2O). The results were as follows: P/Solutol HS15/D_2O-saline, cloud point $> 40°C$; P/Vitamin E TPGS/D_2O-saline, liquid crystalline transition (gelation) $< 42°C$; P/Tween 80/D_2O-saline, cloud point $> 40°C$; P/Cremophor EL/D_2O-saline, cloud point $> 50°C$; P/either Poloxamer/D_2O-saline, gelation $> 50°C$.

^1H NMR peaks from hydrophobic groups shifted to low frequency in the presence of propofol. Table 1 lists the chemical shifts of selected peaks in the 10% (w/v) surfactant/D_2O-saline and 1% (w/v) propofol/10% (w/v) surfactant/D_2O-saline systems (S/D_2O-saline and P/S/D_2O-saline, respectively). The average propofol-induced low-frequency shift for the "hydrophilic" PEO CH_2 peaks was 0.01 ± 0.01 ppm, while for the "hydrophobic" ones it was 0.07 ± 0.05 ppm. In addition, propofol effected either a change of the lineshape or a partial splitting of the PEO peak at 3.7 ppm. The extent of the changes depended on the surfactant.

Propofol + Solutol HS15. The micellar diffusion coefficient of PEO–HS ester in a propofol-free Solutol solution [9.15% (w/w)] was 1.9×10^{-11} m^2 s^{-1}. As an example of propofol solubilization, the system consisting of 1% (w/v) propofol and 10% (w/v) Solutol HS15 in D_2O-saline (P/Sol/D_2O-saline) was studied in detail. Its proton NMR spectrum is shown in Figure 3A,B. The PEO peak near 3.7 ppm experienced a partial splitting in the presence of propofol, which is evident from a comparison of parts B and C of Figure 3. The two peaks from aromatic protons near 7 ppm were used as diffusion and relaxation indicators of propofol. The CH_3 peak at 0.87 ppm and the slowly diffusing component of the PEO peak at 3.73 ppm were used as indi-

cators for the surfactant micelles. Aliphatic peaks at 1.27 ppm (PEO–HS ester) and 1.19 ppm (propofol) overlapped, and only a single T_1 and D could be determined for these peaks. The T_1 and D values determined from the non-overlapping peaks are presented in Table 2. The peak at 1.27/1.19 ppm showed monoexponential longitudinal relaxation in all cases, and the value of D obtained from it (1.42×10^{-11} m^2 s^{-1}) was consistent with those listed in Table 2. The observed value of the diffusion coefficient of propofol was $(1.44 \pm 0.1)\times10^{-11}$ m^2 s^{-1}. The diffusion coefficient of the surfactant (polyethoxylated 12-hydroxystearate) in the propofol-containing solution was $(1.27 \pm 0.1)\times10^{-11}$ m^2 s^{-1}. The NOESY spectrum of the P/Sol/D_2O-saline system revealed strong negative intermolecular NOEs between the aromatic propofol peaks and the Solutol HS15 peaks at 3.73 and 0.87 ppm.

Propofol and other surfactants. Table 3 shows propofol and surfactant diffusion coefficients in each of the propofol/surfactant/D_2O-saline systems. In each of these, ^{1}H PFG NMR diffusion measurements showed the presence of two PEO populations, rapidly and slowly diffusing. In addition to the "fast" PEO population, in the two Poloxamers the polypropyleneoxide (PPO) peak near 1.18 ppm also exhibited two separate diffusion coefficients. In each of the six systems, the Stejskal–Tanner plots of propofol signals were linear. The effective diffusion coefficients were slightly higher than the "slow" diffusion coefficients of the respective surfactants. The values of all the diffusion coefficients were independent of the diffusion interval Δ in the range studied. From a comparison of several measurement methods, the relative standard deviation of the measured diffusion coefficients was estimated to be 5%.

A study of the concentration dependence of the diffusion coefficients of the surfactants and propofol was not made. However, measurements of the Solutol HS15/D_2O-saline

system revealed that the dependence of the micellar D of Solutol on its concentration in D_2O in the range 1–5% (w/v) was significant, i.e. exceeded the standard deviation of the measurement. This means that the values of the diffusion coefficients reported here should be treated as concentration-specific.

Table 4 lists the T_1 values of the two aromatic protons of propofol in three of the studied systems. The standard deviation of the reported values is conservatively estimated at $\pm$30 ms. Propofol T_1 values in the other three systems were less precise but were consistent with the three former systems, that is, near 500 ms.

NOESY spectra were also recorded for the propofol/Tween 80/D_2O-saline system at 22 °C and 35 °C. The sorbitan–propofol intermolecular NOEs were negative at 22 °C and weakly positive at 35 °C. The PEO–propofol NOEs were weakly negative and weakly positive, respectively.

4 Discussion

Although the phase diagrams of surfactant systems can be very complex,[46,47] in this work we focused only on the simple disordered micellar and unimer phases which exist in dilute solutions of surfactants. All of the studied surfactants, with the exception of Poloxamer 188, have critical micellization concentrations well below 1% (w/v) at biologically relevant temperatures. F68, on the other hand, exists in a 10% (w/v) water solution in the unimer form up to 33 °C.[7] The range of surfactants investigated thus permitted a comparison of the micellar and the unimer solubilization of propofol.

As can be expected of high-molecular weight compounds, the room-temperature values of the diffusion coefficients of each of the surfactants in their water solutions were of the order of 10^{-11} m^2 s^{-1} or smaller. The proton longitudinal relaxation times of Solutol HS15 were measured both above and below cmc. The latter values were slightly longer than the former. This is consistent with results reported for surfactants of similar MW,[48] and with the assumption that the rotational reorientation time of a single surfactant molecule lies near the crossover from the extreme-narrowing limit to slow-motion limit. The proton T_1's in each surfactant did not exceed 1 s either above or below cmc, and were in the range 350–700 ms when the surfactants were in micellar form. Literature values of the cmc for each of the studied surfactants are listed in Table 5. Except for Poloxamer 188 (F68), all of the compounds are known to be in the micellar form in water solution in the temperature range 20–40 °C and concentration range 1–15% (w/v).[5,49,50] The presence of electrolytes is known to affect the phase diagrams of surfactant/water systems.[47] However, the effect is not significant at the physiological saline concentration (0.9% = 154 mM NaCl). This was confirmed by our measurements carried out on pure-D_2O solutions; the results were essentially

the same as those for the D_2O-saline solutions discussed below. Each surfactant contains a significant quantity of free PEO whose protons have the same chemical shift as those of the micellar surfactant PEO. Therefore, in diffusion experiments the single PEO ^1H NMR peak corresponded to two non-exchanging populations, micellized and free PEO, and exhibited two diffusion coefficients.

Propofol solubilization: initial observations. In contrast to the macromolecular surfactants, propofol is a small molecule. It is a dark-yellow liquid almost insoluble in water ($\sim$150 mg/L) but soluble in many organic solvents.[2,51] A comparison of the spectrum in Figure 2 with those of the surfactants (cf. Figure 1) revealed that the two aromatic proton multiplets near 7 ppm were always well-separated from all surfactant peaks, and were therefore suitable as indicators of propofol behavior in surfactant solutions. The other peaks overlapped with surfactant peaks either partially or fully. Hence, D and T_1 values measured from the latter were generally less reliable than those measured from the former.

The first indicators that the solubilization involved direct molecular association between propofol and the surfactants were the systematic low-frequency shift of ^1H NMR signals from hydrophobic protons (Table 1) and the changes of the PEO lineshape induced by propofol. The average low-frequency shift in the presence of 1% (w/v) propofol for the "hydrophilic" and "hydrophobic" peaks was 0.01 $\pm$ 0.01 ppm and 0.07 $\pm$ 0.05 ppm, respectively. Although the possibility of a comparison of absolute shifts of such magnitude, when the referencing is done on the temperature- and pH-dependent HDO peak, is questionable, the *relative* shift of one group of protons versus the other is unambiguous. The hydrophobic non-EO CH_2 and CH_3 protons were thus shifted to low frequency considerably more than the relatively hydrophilic

EO CH_2 protons were. This is consistent with the former being in contact with domains possessing a more positive magnetic susceptibility than that of D_2O, which is expected of an aromatic compound like propofol.[52]

Propofol + Solutol HS15. Diffusion studies of Solutol HS15 revealed that the ethylene oxide peak near 3.7 ppm exhibited two diffusion coefficients which differed roughly by about an order of magnitude and had population ratios of approximately 2(fast):1(slow). The two observed diffusion coefficients were attributed to the free PEO and the PEO blocks of the micellized surfactant, polyethoxylated 12-hydroxystearate. The diffusion coefficient of PEO–HS ester measured from the signal at 0.85 ppm was consistent with the "slow" PEO D to within 3% (see Table 2).

T_1 values of propofol indicate the local viscosity of propofol domains. In bulk-like propofol droplets, propofol protons would have T_1 values of approximately 1 s. Propofol molecules dispersed in a micellar core would experience a greater local viscosity and therefore have longer reorientation times and shorter T_1 values. T_1 values of propofol protons thus allow us to distinguish between bulk-like propofol and propofol dispersed in the micellar core. (This can be compared to the hydration test in W/O microemulsions which has been used to distinguish between bulk-like "active" water and water dissolved in oil.[53]) In the system propofol/Solutol HS15/D_2O-saline, the T_1 values of propofol protons are considerably shorter than in bulk propofol, indicating that propofol domains inside the micelles do not possess a bulk-like viscosity. On the other hand, a partial splitting of the PEO peak was present in this system (cf. Figure 3B,C). The diffusion coefficient of propofol-loaded PEO–HS micelles was smaller than the micellar D in the system Solutol HS15/D_2O-saline (1.9×10^{-11} m^2 s^{-1}) by a factor of 1.5. This proves that the uptake of propofol increased the size of the surfac-

tant micelles. The observed specific solubilization capacity of $\geq$10% is plausible for micellar solubilization.[54,55]

The observed diffusion coefficient of propofol was close to, but slightly higher than, the observed micellar diffusion coefficient of PEO–HS ester (1.9×10^{-11} m^2 s^{-1}). For a single system, this could be attributed to an experimental error. However, the results for other surfactants, presented in Table 3, revealed that this was a consistent phenomenon. We surmise that the explanation lies in the partitioning and fast chemical exchange of propofol molecules between the micelles and the extramicellar medium. The solubility of propofol in water ($\sim$150 mg/L) is sufficiently high to account for the difference between the two diffusion coefficients. However, the presence of intermolecular NOEs between PEO and propofol indicates that the extramicellar propofol is likely to be associated with the free PEO blocks. This model is illustrated in Figure 4. The observed propofol diffusion coefficient is thus the weighted average of the diffusion coefficients of micelles and the free PEO.[45] The respective values correspond to approximately 1% of propofol residing in the latter. This outcome is plausible considering that PEO blocks constitute the relatively hydrophylic head of the Solutol molecule, while the 12-hydroxystearic acid moiety forms the hydrophobic tail.

Propofol and other surfactants. Free PEO was present in all of the studied surfactant solutions. There was a loose correlation between its diffusion coefficient and the size of the PEO block in the surfactant molecule. The diffusion coefficient of HDO was in the range (1.1–1.5)$\times10^{-9}$ m^2 s^{-1} for all samples, meaning that the values of the effective hydrodynamic viscosities of the solutions were within 40% of each other. In the Poloxamer solutions, the two diffusion coefficients measured from the PPO peak near 1.18 ppm were interpreted as belonging to the free PPO and the micellar PPO

populations, respectively.

With the exception of the Poloxamers, the observed diffusion coefficients of propofol (Table 3) were very close to but a few per cent higher than the values of the micellar diffusion coefficients of the respective surfactants. The explanation is the same as in the case of Solutol HS15. Propofol molecules essentially resided in the micelles. However, $\sim$1% of the total propofol was associated with free PEO. The latter possessed a relatively large D value, which caused the observed diffusion coefficient of propofol to be slightly larger than that of the micelles.

In the case of the Poloxamers, the more hydrophobic free PPO was also present in the solution. This further increased the apparent diffusion coefficient of propofol. The large difference between the apparent D of propofol and the micellar D of the surfactant can be misleading. Assuming that half of all PO is in the free-PPO form and that the affinity of propofol to free PPO is much greater than to the free PEO, $\sim$15% of propofol needs to be associated with the free PPO in order to explain the apparent propofol D values in the two Poloxamer solutions. This would correspond to an extramicellar concentration of propofol of 0.15% (w/v), which significantly exceeds its solubility in water, 0.015% (w/w).[9] This supports the hypothesis that the extramicellar propofol is associated with PEO or PPO blocks rather than present in the free form.

Poloxamer 188 is a special case because it does not micellize under the conditions used in the present study. This was reflected in its "slow" D being almost an order of magnitude greater than that of F127, although the lengths of the unimers differ by only a factor of 1.4–1.5. This implies that micelles were indeed absent from the Poloxamer188/propofol/D_2O-saline system, and the "slow" D was that of the unimer.

The value of the observed diffusion coefficient of propofol in this system was consistent with the foregoing model; the measured values of the unimer diffusion coefficient; and with the assumption that the majority of propofol molecules are associated with the Poloxamer188 unimers. Therefore, Poloxamer188 solubilized propofol despite not being able to form micelles under the investigated conditions. At the same time, the copolymeric unimer is a "mini-micelle" in its own right, because it possesses a hydrophobic (PPO) and two hydrophilic (PEO) blocks. These blocks act as a core and a corona of the "mini-micelle", respectively.

Micellar size and hard-sphere reorientation time can be formally estimated from the micellar diffusion coefficients using the Stokes-Einstein model as $r = kT/6\pi\eta D$, $\tau_r = \eta V/kT$, where k is Boltzmann's constant, T is the temperature; η, solvent viscosity; τ_r, molecular reorientation time; and r and V are molecular hydrodynamic radius and volume, respectively. These estimates, assuming that the viscosity of the solution is that of D_2O, 1.157cP, are given in Table 6. However, they are not indicative of actual molecular reorientation times, as will be evident from the following discussion. Because there is no direct relationship between the micellar hydrodynamic radius and aggregation number,[6] the values in Table 6 should not be used to estimate the latter.

Consistent with the micellar solubilization of propofol is the shortening of its proton T_1 values in surfactant solutions. It is clear that its uptake by surfactant micelles caused a lengthening of the molecular reorientation time of propofol; however, it was problematic to estimate by how much, based on the available experimental information. The reorientation time of propofol in $CDCl_3$ was estimated from propofol's molecular size and solvent viscosity at $\sim$0.03 ns. Using the well-known expression

for the contribution to $1/T_1$ from dipolar relaxation by like spins, we could verify that no value of rotational correlation time τ_c produced a T_1 shortening from 3.5 s in $CDCl_3$ to $\sim$600 ms (see Table 4). Therefore, proton relaxation in propofol must have had contributions from mechanisms other than intramolecular dipolar interaction, which precluded a simple estimate of τ_c. At the same time, it is clear that the hard-sphere micellar reorientation times from Table 6 are several orders of magnitude greater than realistic values of the rotational correlation times of either propofol or the surfactants. Therefore, the only conclusions that we can draw are: (1) that molecular reorientation of propofol and the surfactants within the micelles is determined by intra-micellar degrees of freedom rather than by rigid-sphere micelle reorientation; and (2) that proton relaxation in propofol in the surfactant solutions is more complex than a single-mechanism intramolecular homonuclear dipolar relaxation.

As discussed above, the room-temperature intermolecular NOEs between Solutol HS15 and propofol were prominently negative. For the system propofol/Tween 80/D_2O-saline, they were negative at 22 °C and weakly positive at 35 °C. The crossover point from the positive to the negative NOE corresponds to the molecular reorientation time of $\tau_{crit} = \sqrt{5}/2\omega$, that is, 0.44 ns for proton–proton NOEs at 400MHz. Again, it is clear that propofol and surfactant molecules undergo a facile mutual reorientation within the swollen micelles, as its timescale is several order of magnitude smaller than the hard-sphere reorientation time values shown in Table 6. The temperature trend in the system P/T80/D_2O-saline is therefore consistent with the shortening of molecular reorientation times as the temperature is increased.

5 Conclusions

In this work we aimed to characterize various physical-chemical factors associated with propofol–surfactant systems. The main conclusions were: (1) Neither the chemical shift nor the T_1 of free PEO blocks are resolved from those of the micellar PEO forming the hydrophilic heads of respective surfactants. However, the free PEO manifests itself in diffusion experiments as a fast-diffusing component of the methylene ^{1}H NMR peak (3.7 ppm). (2) Micellar diffusion coefficients (or, in the case of non-micellar Poloxamer 188, the unimer) were approximately an order of magnitude smaller than those of the fast-diffusing PEO or PPO. (3) The two values were well-resolved in Stejskal–Tanner diffusion plots. (4) Each of the six surfactants solubilizes propofol with the specific solubilization capacity of at least a 0.1 g/g in the surfactant concentration range 0–10% (w/v). (5) In solutions of Solutol HS15, Cremophor EL, Tween 80, and Vitamin E TPGS, approximately 1% of the total propofol was partitioned into the free PEO, with the rest residing in surfactant micelles. (6) In solutions of the two Poloxamers, approximately 15% of total propofol was associated with the free PPO, with the rest associated with Poloxamer. (7) In each case, propofol exhibited a single Δ-independent diffusion coefficient which was the weighted average of the two populations, which suggests the presence of fast chemical exchange between them. (8) The stability of solutions at both room temperature and 4°C and high ($> 40°$) clouding point and gelation temperatures suggest the possibility of their use in pharmaceutical formulations.

The practical aim of the study was to investigate novel micellar formulations of propofol potentially appropriate for intravenous administration. Many clinically relevant issues were outside the scope of the present study. These include, among others, sus-

ceptibility to bacterial growth; interaction with plasma proteins; hemo- and hepatotoxicity; interaction with cell membranes; pain on injection; and interaction with those metabolites which can be present in the body in high concentrations (such as urea[56]). Some nonionic surfactants (such as Triton or Brij) were also outside the scope of this work, but would probably be good candidates of a future study.

However, at least two clinically relevant issues are noted on the basis of the results presented here. The first is the issue of micellar versus unimer solubilization of the drug. It appears that the surfactant's facility for unimer solubilization of propofol could be a prerequisite for its intravenous use under some conditions, namely, when the uptake of the drug is slow and the injection results in a dilution of the surfactant to a concentration below its cmc. At least one surfactant, Poloxamer 188, is capable of unimer solubilization of propofol. Significant solubility enhancements of hydrophobic compounds have been noted for other Poloxamers at concentrations below their respective cmc values.[11] However, the unimer solubilization capacity of the other surfactants is unclear and requires further investigation.

The second issue is that of the pain experienced by patients on intravenous administration of propofol. With Diprivan emulsion, the pain has been attributed to the free propofol present in blood due to its non-zero solubility in aqueous media. In this respect, the partitioning of propofol into the free ethylene oxide is a negative factor, because free PEO-associated propofol is likely to contribute to the pain experienced by patients. We suggest that the use of purified surfactants, from which the free PEO has been removed chromatographically or otherwise, could provide for a smaller concentration of extramicellar propofol. This will be the subject of further study.

Acknowledgements. P.W.K. and K.I.M. acknowledge the support of an ARC-SPIRT grant. The authors thank Mr. Bill Lowe and Dr. W. A. Bubb for technical and NMR spectroscopic assistance, respectively.

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FIGURE CAPTIONS

Figure 1. Proton NMR spectra of: (A) Tween 80; (B) Vitamin E TPGS; (C) Poloxamer 407 (all at 10% (w/v) concentration in D_2O-saline). In (A) and (B), the biggest peak (3.7 ppm) is a superposition of –CH_2– peaks from the micellized and the free PEO blocks. In (C), it is a superposition of the same peaks from the same two PEO populations as well as –CH– peaks both from the micellar and the free PPO blocks. The peak near 0.9 ppm in (A) and (B) is from aliphatic CH_3 groups. The peak near 1.3 ppm in (A) belongs to aliphatic (non-EO) –CH_2– groups. The peak near 1.1 ppm in (C) is from PPO CH_3 groups. The smaller peaks in the aliphatic region in (A) and (B) belong to various moieties of the hydrophobic sorbitan and Vitamin E tails, respectively.

Figure 2. Chemical structure of propofol and its ^{1}H NMR spectrum in a $CDCl_3$ solution. Assignments (400 MHz, δ): 7.15 (d, J = 7.6 Hz, 2H, Ar H_3 and H_5), 7.00 (t, J = 7.6 Hz, 1H, Ar H_4), 4.89 (br s, 1H, OH), 3.25 (septet, J = 6.9 Hz, 2H, –C*H*$(CH_3)_2$), 1.36 (d, J = 6.9 Hz, 12H, CH_3),

Figure 3. (A) Proton NMR spectrum of the system 1% (w/v) propofol/10% (w/v) Solutol HS15/D_2O-saline (P/Sol/D_2O-saline). This spectrum is representative of other P/surfactant/D_2O-saline systems studied. The solids arrows (peaks a, b) show propofol peaks which were used for the determination of its diffusion coefficient. The dashed arrows (peaks c, d) show other propofol peaks. Peak e belongs to PEO–HS ester; it was not used because of the overlap with the propofol peak.
(B, C) Detail of the PEO lineshape in propofol/Solutol HS15/D_2O-saline and Solutol HS15/D_2O-saline, respectively. Propofol induced a partial splitting of the PEO peak.

Figure 4. Reaction scheme depicting the association of propofol with surfactant micelles and free PEO blocks in surfactant solutions. Based on the values of the observed diffusion coefficients shown in Table 3, approximately 99% of propofol in non-Poloxamer solutions is micellized. In Poloxamer solutions, PEO is replaced by PPO and the fraction of micellized propofol was estimated to be approximately 85%.

TABLES

Table 1: Chemical shifts (ppm) of several ^{1}H NMR peaks of propofol-free and propofol-containing surfactant solutions in D_2O-saline. The HDO peak was used as a reference (set nominally to 4.8 ppm).

Surfactant	10% (w/v) S/D_2O-saline			1% (w/v) P/10% (w/v) S/D_2O-saline		
	PEO/PPO CH_2 [a]	non-EO CH_2 [b]	PPO or non-PPO CH_3 [b]	PEO/PPO CH_2 [a]	non-EO CH_2 [b]	PPO or non-PPO CH_3 [b]
F68	3.722	–	1.188[c]	3.720	–	1.169 and 0.994[c]
F127	3.724	–	1.170[c]	3.710	–	1.050[c]
Sol15	3.721	1.325	0.928[d]	3.728	1.273	0.868[d]
T80	3.720	1.323	0.915[d]	3.708	1.256	0.857[d]
CEL	3.722	1.321	0.920[d]	3.707	1.250	0.851[d]
VE	3.712	1.280	0.881[d]	3.689	1.270	0.853[d]

[a] "hydrophilic"

[b] "hydrophobic"

[c] PPO

[d] aliphatic non-PPO

Table 2: ^{1}H NMR longitudinal relaxation times and ^{1}H-determined diffusion coefficients in the system 1% (w/v) propofol/10% (w/v) Solutol HS15/D_2O-saline. The standard deviation of the reported T_1 values was $\pm$30 ms; that of the diffusion coefficient values was $\pm 0.07 \times 10^{-11}$ m^2 s^{-1}.

δ (ppm)	Compound	T_1 (ms)	D (m^2 s^{-1})
6.93	P	570	1.42×10^{-11}
6.74	P	570	1.47×10^{-11}
3.73	Sol15	590	1.25×10^{-11} (28%)[a] 1.39×10^{-10} (72%)[b]
0.87	Sol15	560	1.29×10^{-11}

[a)] 12-hydroxystearate-bound micellar PEO

[b)] free PEO

Table 3: Values of the apparent diffusion coefficients of propofol and surfactants in the respective 1% (w/v) propofol/10% (w/v) surfactant/D_2O-saline systems. The relative standard deviation of the diffusion coefficient values was $\pm$5%.

Surfactant	D (m^2 s^{-1})			
	Propofol	Surfactant (slow component)	Fast PEO component	Fast PPO component
Sol15	1.44×10^{-11}	1.27×10^{-11}	1.39×10^{-10}	n/a
T80	1.64×10^{-11}	1.42×10^{-11}	3.72×10^{-11}	n/a
CEL	1.47×10^{-11}	1.40×10^{-11}	1.06×10^{-10}	n/a
VE	1.20×10^{-11}	1.04×10^{-11}	3.59×10^{-11}	n/a
F68	7.10×10^{-12}	5.43×10^{-12}	2.03×10^{-11}	1.62×10^{-11}
F127	2.65×10^{-12}	6.85×10^{-13}	2.05×10^{-11}	1.55×10^{-11}

Table 4: Longitudinal relaxation time (T_1) of aromatic protons in solubilized propofol. The typical standard deviation of the T_1 values was $\pm$30 ms.

Surfactant	T_1 (ms)	
	H_3, H_5	H_4
Sol15	570	570
F68	630	710
F127	560	610

Table 5: Literature values of the critical micellization concentration of the studied surfactants.[a]

Surfactant	cmc (% w/v)	cmc (mM)	*T* (°C)	Reference
F68	15 7	17.9 8.333	27 40	7
F127	4 0.7 0.008	3.174 0.555 0.006	20 25 40	7
Sol15	0.02	0.21	25	57
T80	0.0013	0.01	25	58
CEL	0.01	0.04	25	8
VE	0.02	0.13	37	50

[a)] Abbreviations: F68, Poloxamer 188 (Lutrol F68); F127, Poloxamer 407 (Lutrol F127); Sol15, Solutol HS15; T80, Tween80 (Crillet 4 HP, Polysorbate80); CEL, Cremophor EL; VE, Vitamin E TPGS.

Table 6: Estimated micellar diameter and rigid-sphere micellar reorientation time for the studied surfactants.[a] Rigid-sphere reorientation times greatly exceeded realistic values of molecular correlation times of both the surfactant and propofol (refer to Discussion). The nominal error intervals were calculated assuming that the relative standard deviation of the D values was 5%.

Surfactant	d (nm)	τ_r (ms)
Sol15	15 ± 0.8	3.8 ± 0.5
T80	13 ± 0.7	2.7 ± 0.4
CEL	13 ± 0.7	2.8 ± 0.5
VE	18 ± 0.9	6.9 ± 1.0
F68	35 ± 1.8	49 ± 7
F127	274 ± 14	24000 ± 3500

[a)] Obtained using the Stokes–Einstein model (see text). The viscosity of the solution taken as $\eta(D_2O) = 1.157$ cP,[59] $T = 23\ ^\circ$C.

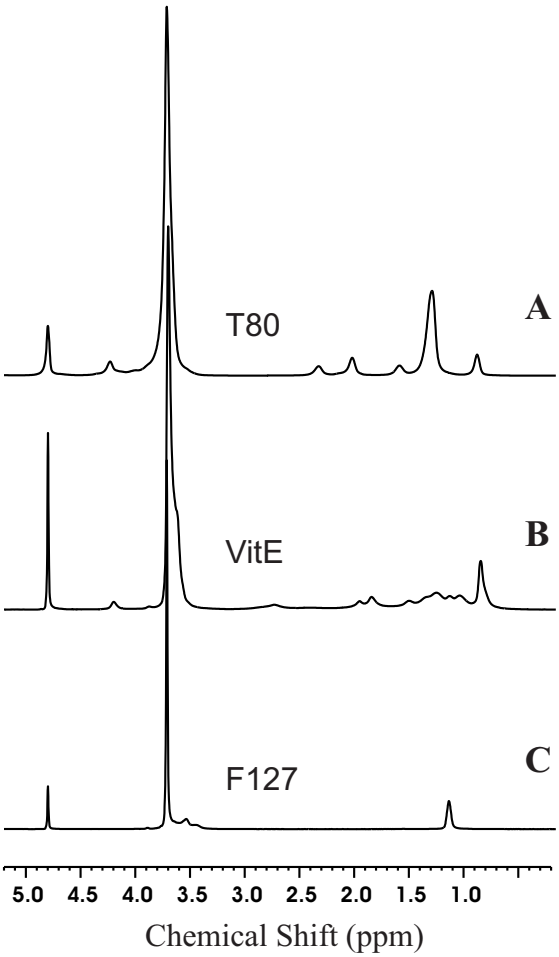

Figure 1, Momot et al, Propofol Solubilization

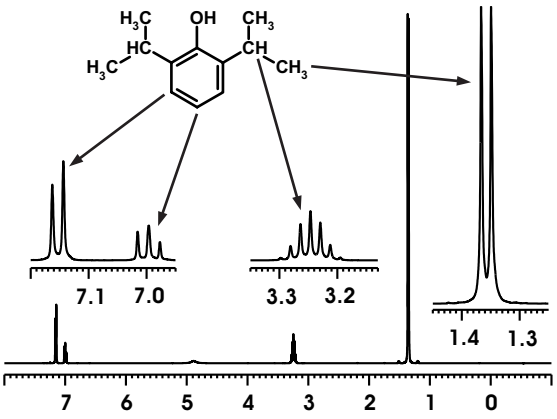

Figure 2, Momot et al, Propofol Solubilization

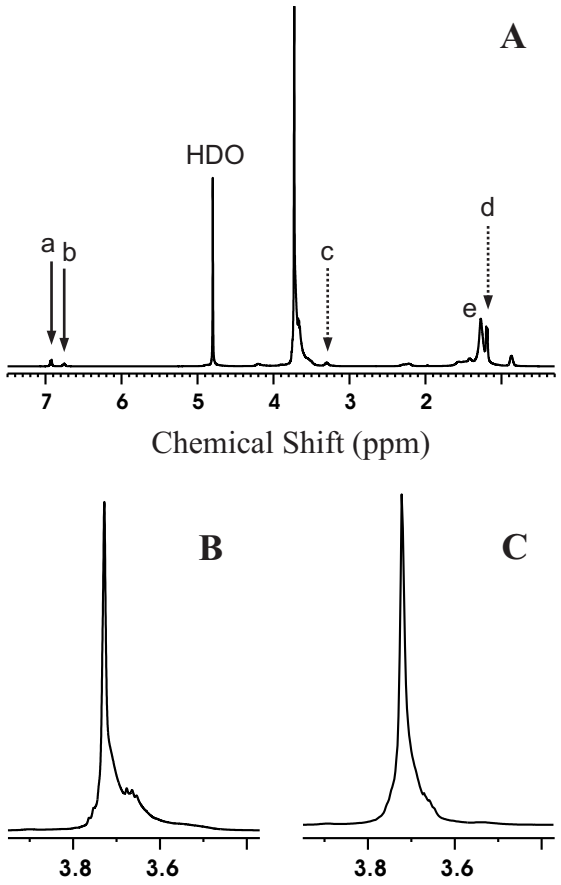

Figure 3, Momot et al, Propofol Solubilization

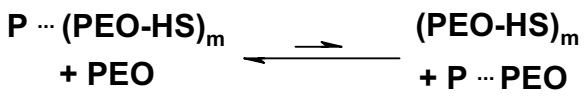

Figure 4, Momot et al, Propofol Solubilization